BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 July 2001 (26.07.2001)

PCT

(10) International Publication Number
WO 01/52897 A2

(51) International Patent Classification[7]: A61K 47/12, 47/10, 47/22, 47/18

(21) International Application Number: PCT/IN01/00007

(22) International Filing Date: 19 January 2001 (19.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
46/DEL/2000 21 January 2000 (21.01.2000) IN

(71) Applicant *(for all designated States except US)*: **PANACEA BIOTEC LIMITED** [IN/IN]; B-1 Extn./A-27, Mohan Co-operative, Industrial Estate, Mathura Road, New Delhi 110 044 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SINGH, Amarjit** [IN/IN]; Panacea Biotec Limited, B-1 Extn./A-27, Mohan Co-operative, Industrial Estate, Mathura Road, New Delhi 110 044 (IN). **JAIN, Rajesh** [IN/IN]; Panacea Biotec Limited, B-1 Extn./A-27, Mohan Co-operative, Industrial Estate, Mathura Road, New Delhi 110 044 (IN).

(74) Common Representative: **JAIN, Rajesh**; Panacea Biotec Limited, B-1 Extn./A-27, Mohan Co-operative, Industrial Estate, Mathura Road, New Delhi 110 044 (IN).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/52897 A2

(54) Title: THERAPEUTIC ANTI-INFLAMMATORY AND ANALGESIC COMPOSITION CONTAINING SELECTIVE COX-2 INHIBITOR DRUGS FOR USE TRANSDERMALLY AND A PROCESS FOR THE MANUFACTURE THEREOF

(57) Abstract: A therapeutic anti-inflammatory and analgesic composition for topical/transdermal use which comprises: Selective Cox-2 inhibitor drugs from 0.1% to 40% w/w and percutaneous absorption enhancing vehicle/base from 60% to 99.9% w/w. Optionally Gelling agent/thickening agent (0% to 60% w/w) surfactant (0% to 20% w/w), Neutralizing agent/pH adjusting agent (0% to 5% w/w) may be added to the said composition.

THERAPEUTIC ANTI-INFLAMMATORY AND ANALGESIC COMPOSITION CONTAINING SELECTIVE COX-2 INHIBITOR DRUGS FOR USE TRANSDERMALLY AND A PROCESS FOR THE MANUFACTURE THEREOF

TECHNICAL FIELD

This invention relates to novel therapeutic anti-inflammatory and analgesic pharmaceutical compositions containing Selective COX- 2 inhibitors drugs for use transdermally and a process for the manufacture thereof.

BACKGROUND OF THE INVENTION

For a drug to be absorbed transdermally, it has to travel through various layers of the skin before reaching the site of action.

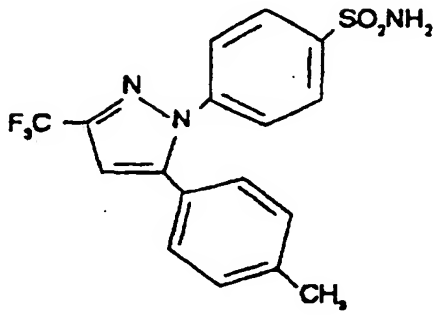
The layers of the skin are different in nature-some are hydrophilic while some are lipophilic (Montagna W. Parrakhal PF: The structure and Function of the skin, 3rd ed. Academic press, New York, 1974). Accordingly, any drug which is used transdermally must possess both hydrophilic and lipophillic properties. COX- 2 inhibitor drugs such as Celecoxib and Rofecoxib are a highly hydrophobic drugs and consequently they are considered poor candidate for transdermal absorption. When applied to the skin, these are absorbed in very minute quantities or not absorbed at all.

A transdermal route for administration of anti-inflammatory agents offers various advantages over the oral route such as lower dosage, less toxicity/side effects, no G I irritation, no dose dumping in the body and it is more site specific (Chien YW: Novel Drug Delivery System, Marcel Dekker, New York, 1982).

The identification of two cyclooxygenase (COX) enzymes has been a tremendous advance in understanding the role of prostaglandins in inflammation and the actions of nonsteroidal anti-inflammatory drugs (NSAIDs.) COX-1 activity appears to be related to "constitutive" or "house-keeping" functions in the gastric mucosa, kindney and platelets. COX-2 activity is "inducible" and generally occurs in response to a specific stimulus to enhance inflammatory actions. Current NSAIDs inhibit both COX-1 and COX-2, although the clinical benefit of NSAIDs appears to be associated with inhibition of COX-2 activity. The inhibition of COX-1 activity by NSAIDs is related to adverse side effects in general, particularly gastrointestinal toxicity. Recently, COX-2 selective inhibitors have been developed. Current data would suggest that by inhibiting COX-2 action, these agents may have efficacy similar to that of standard NSAIDs and that by not inhibiting COX-1 activity, they may have less toxicity than standard NSAIDs. Thus, these actions indicate that COX-2 selective inhibitors will have similar clinical efficacy to the traditional NSAIDs with fewer adverse side effects.

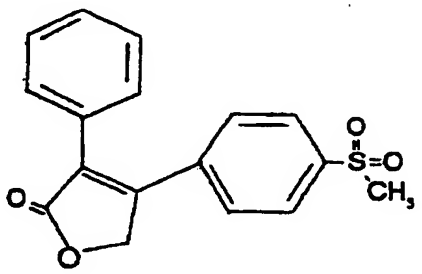
Celecoxib is a known selective COX-2 inhibitor having analgesic and anti-inflammatory activity, but which has the drawback of having unfavourable chemical-physical characteristics; the main obstacle to the use of celecoxib in topical formulation is in fact its insolubility in water and, on the other hand, its poor solubility in the solvents/raw materials usually employed in such formulation.

The chemical structure of Celecoxib and Rofecoxib are given hereinbelow alongwith their chemical names:-



Celecoxib

Celecoxib:- p[5-p-Tolyl-3-(trifluoromethyl) pyrazol-1-yl) benzenesulfonamide.



Rofecoxib

Rofecoxib:- 4-[4-(methyl sulphonyl) phenyl]-3-phenyl-2(5H)-furanone.

In the Patent Application PCT Publication No. PCT/US94/12720 Celecoxib is disclosed. However, no transdermal composition of this Drug is disclosed.

It is an object of the present invention to provide a therapeutic composition containing COX-2 inhibitor in combination with other compounds which alter the hydrophobic property of Nimesulide and a process for the manufacture thereof thus making it possible for the composition to be used for direct application on the skin for the treatment of inflammation through transdermal absorption.

It is a further object of the present invention to provide a novel therapeutic composition containing COX-2 invention in combination with other compounds which alter the physico-chemical property of COX-2.

SUMMARY OF THE INVENTION

The present invention provides a Novel Therapeutic Anti-inflammatory and Analgesic Pharmaceutical composition for topical use which comprises :

1. Selective COX-2 inhibitor drugs : 0.1% to 40% w/w.
2. Percutaneous absorption enhancing vehicle base. : 60% to 99.9% w/w

The said Percutaneous enhancing vehicle base comprises :

1. Percutaneous enhancer : 0.5% to 60% w/w
2. Surfactant : 0.0% to 20 % w/w
3. Gelling agent/Thickening agent : 0.0% to 60% w/w
4. One or more vehicle/base : 2% to 98% w/w.

Preferably the percutaneous enhancing base comprises :

1. Percutaneous enhancer : 6% to 15% w/w
2. Surfactant : 0.5% to 12% w/w
3. Gelling agent/Thickening agent : 0.5% to 19% w/w
4. One or more vehicle/base : 5% to 60% w/w.

One or more percutaneous enhancers can be used in compositions according to this invention. One or more surfactants can be used in compositions according to this invention. One or more gelling agents/thickening agents can be used in compositions according to this invention.

Besides the above disclosed ingredients the composition for topical use also comprises a neutralizing agent/pH adjusting agent such as herein described in the range of 0.0% to 5.0%.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, it has been found that it is possible to deliver a highly hydrophobic drugs such as COX-2 inhibitor drugs to the site of action through a transdermal route. The present invention involves the process of incorporation of COX-2 inhibitor drugs in a formulation which can transport the drug through the skin barriers, in intact condition to the site of action.

Preferably the percutaneous enhancing base comprises :

1. Percutaneous enhancer : 6% to 15% w/w
2. Surfactant : 0.5% to 12% w/w
3. Gelling agent/Thickening agent : 0.5% to 19% w/w
4. One or more vehicle/base : 5% to 60% w/w.

Preferably the COX-2 inhibitor drugs are in the range of 0.2% to 20% w/w. More preferably the composition for topical use also comprises a Neutralising agent/ph adjusting agent as herein described in the range of 0.0% to 2.0%.

The novel Therapeutic Anti-Inflammatory and Analgesic Composition for topical use according to the present invention, is prepared by the process which comprises the following steps :

(a) 0.5% to 60% w/w of a Percutaneous enhancer, as herein described, is mixed with 2.0% to 98% w/w of one or more Vehicle or base, as herein described, in a container by stirring and to the mixture obtained 0.1% to 40% w/w of COX-2 inhibitor drugs are added and stirred till completely dissolved.

(b) 0% to 20 % w/w of a Surfactant, as herein described, 0.2% to 60% w/w of a Gelling agent/thickening agent, as herein described, and 0.5% to 60% w/w of one or more Vehicle/Base, as herein described, are mixed in a homogeniser to obtain a homogenised mixture.

(c) The mixture obtained in step (a) is added to the homogenised mixture obtained in step (b) under stirring without vortex formation to avoid aeration. The mixture is neutralised or its pH adjusted by addition of 0.0% to 5.0% of neutralizing agent or a pH adjusting agent to being the pH of the product on the acidic side, as herein described, with slow stirring resulting in the preparation of the desired Anti-inflammatory and Analgesic Composition.

As Percutaneous enhancer any chemical can be used which interacts with the stratum corneum layer of the mammalian skin causing reversible change in its barrier properties.

Preferably, as Percutaneous enhancer any known Percutaneous enhancer may be used preferably a C_{12-24} mono or poly-unsaturated fatty acids such as vaccenic, cis-vaccenic, Linoleic, Linolenic, elaidic, oleic, petroselinic, erucic or nervonic acid or any of their corresponding alcohols, especially oleic acid or oleyl alcohol or 1-dodecylazacycloheptane-2-one also known as azone;sulphoxides like dimethylsuphoxide, n-decyl methylsulphoxide; Amides like dimethylacetamide, dimethylformamide and N, N-diethylm-toluamide; Pyrrolidones like 2-pyrrolidone and N-methyl-2 Pyrrolidone, volatile oils like oil of citrata, mentha, winter green.

As surfactant, any pharmaceutically acceptable hydrophilic or lipophilic surfactant or mixture thereof may be used, especially suitable for this purpose are the reaction products of natural or hydrogenated vegetable oils and ethylene glycol i.e. polyoxyethylene glycolated natural or hydrogenated vegetable oils, e.g. polyoxyethylene glycolated natural or hydrogenated castor oils; especially various tensides available under the trade name CREMOPHOR particularly CREMOPHOR RH 40 and CREMOPHOR EL. Also suitable for use are the various surfactants available under the trade name NIKKOL e.g. NIKKOL HCO-60.

Polyoxyethlene-Sorbitan fatty acid esters e.g. mono and trilauryl, palmityl, stearyl and oleyl esters e.g. those available under the trade name TWEEN preferably TWEEN 40 and TWEEN 80.

Polyoxyethylene-polyoxypropylene block copolymers e.g. especially those available under the trade name POLOXAMER preferably POLOXAMER 188.

Polyoxyethylene fatty acid esters, for example polyoxyethylene stearic acid esters, commercially available under the trade name MYRJ as well as polyoxyethylene fatty acid esters commercially available under the trade name CEIIOL HE;

Propylene glycol mono-and di-fatty acid esters such as propylene glycol dicaprylate, propylene glycol dilaurate, propylene glycol hydroxysterate, pripylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleater, propylene glycol stearate;

Examples of suitable lipophilic surfactants include trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols. Preferred are products obtained by trans-esterification of 2 molar parts of natural vegetable oil triglycerides with one molar part of polyethylene glycol (e.g. having an average molecular weight of from 200 to 800). Various forms of such trans-estrification product are commercially available under the trade name LABRAFIL, preferably LABRAFIL M 1944 CS;

Sorbitan fatty acid esters commercially available under the trade name SPAN including Sorbitan monolauryl, monopalmityl, -monostearyl, -tristearyl-monooleyl and –trioleyl esters;

Monoglycerides e.g. Glycerol monooleate, glycerol monopalmitate and glycerol monostearate commercially available under the trade names MYVATEX, MYVAPIEX and MYVEROL.

As Gelling Agent/Thickening agent, any known such pharmaceutically acceptable agent may be used including synthetic or semi-synthetic polymeric materials, polyacrylate and polyacrylate co-polymeric resins e.g. polyacrylic acid and polyacrylic acid/methacrylic acid resins, commercially available under the trade name CARBOPOL, particularly CARBOPOL 934, 940 and 941 and EUDRAGIT, particularly EUDRAGIT E, L, S, RL, and RS;

Cellulose and cellulose derivatives including alkyl celluloses e.g. methyl-, ethyl-, and propyl-celluloses; hydroxyalkyl-celluloses e.g. hydroxypropyl cellulose, hydroxypropyl alkylcellulose such as hydroxypropyl-methyl-cellulose, acylated celluloses e.g. cellulose-acetates, cellulose acetate phthalates and salts thereof such as sodium carboxymethyl cellulose;

Polyvinyl resins including polyvinylacetates and alcohols as well as other polymeric materials including alginates e.g. alginic acid and salts thereof e.g. sodium alginate and propylene glycol alginate.

As Neutralising/pH adjusting agent any such conventional such agent may be used including sodium bicarbonate, sodium hydroxide, potassium hydroxide, borax, disodium hydrogen phosphate and sodium dihydrogen phosphate. Preferably polar organic amines like diethylamine, diisopropanolamine, trithylamine and triethanolamine may be used, acidifying agents including hydrochloric acid, lactic acid, malic acid, tartaric acid and the like may also be used.

As vehicles/base, the following may be used :

Pharmaceutically acceptably lower (having C_{1-5}) alkanols, particularly ethanol; water soluble macrogels like polyethylene glycol having an average molecular weight from 200 to 600: 1, 2-propylene carbonate, propane-1, 2-diol and 1, 2-propylene glycol; glycerol triacetate or (1,2,3,)-triacetin; lower ketones, particularly acetone and 1,2,3 – propanetriol may be incorporated. Water in varying concentration may be added to provide the requisite hydrophilic nature to the composition.

Pharmaceutically acceptable C_{1-5} alkyl or tetra hydrofurfuryl; di or partial ether of a low molecular weight mono or polyoxy-alkanediol particularly those available under the trade names TRANSCUTOL and GLYCOFUROL.

As the base having lipophilic properties for the preparation of emulsions, fatty acid triglycerides, preferably medium chain fatty acid triglycerides; vegetable oils like coconut oils, olive oil, castor oil and their derivatives; and ethyl oleate may be used.

As base, for the preparation of the said therapeutic composition in the form of an ointment, fatty acids, fats, oils and waxes of animal origin like bees wax, spermacetii, wool fat, waxes of vegetable origin or mineral origin like hard, soft and liquid paraffin may be used.

The topical dosage forms are formulated suitably such that the resultant product is easy to apply and is non-staining.

For the therapeutic composition in form of an aerosol formulation for topical applications, pharmaceutically acceptable propellants may be used such as chlorofluoro carbons e.g. the Propellant 11, Propellant 12, Propellant 114; Hydrocarbon propellants like n-butane, isobutane and propane; compressed gas propellants e.g. Nitrous oxide, carbon dioxide, and nitrogen.

The novel therapeutic composition according to the present invention may be used in the following forms :

1. Topical gel.
2. Oil-in-water or water-in-oil emulsion or micro-emulsion or cream.
3. Solution for topical applications.
4. Ointment.
5. Aerosol formulation for topical applications.

The therapeutic composition according to the present invention may be applied on the skin by utilising a physical form of energy like electrical energy or ultrasonic energy to effect better percutaneous absorption of the drug.

The invention will now be described with reference to the foregoing examples :

EXAMPLE 1

Preparation of topical gel dosage form

Sl.No.	Component	Quantity
1.	Celecoxib	2.00 g
2.	Dimethylacetamide	22.0 g
3.	Ethyl Alcohol	40.0 g
4.	Acetone	10.0 g
5.	Cremophor RH 40	4.0 g
6.	Propylene glycol	38.0 g
7.	Polyethylene glycol 400	48.8 g
8.	Carbopol 934	4.0 g
9.	Water	30.0 g
10.	Diethylamine	1.2 g
	Total	200.0 g

Step (a) Dimethylacetamide is mixed with ethyl alcohol and acetone at 30°C. in a container with stirring. To the mixture obtained Celecoxib is added and stirred till completely dissolved.

Step (b) Propylene glycol, polyethylene glycol 400 and water are mixed in homogenizer. To the homogenised mixture obtained, 1.5% w/w of carbopol 934 is added in small amounts at a time at room temperature and the speed of the homogenizer is kept at approximately 1500 – 2000 rpm.

Step © The mixture obtained in step (a) is added to the mixture obtained in step (b) under stirring without vortex formation to avoid aeration preferably under vacuum (25 mm of Hg). The mixture obtained is neutralised by slow addition of diethylamine with slow stirring at a temperature of 25° - 30°C and under vacuum (25 mm of Hg) to affect gel formation.

EXAMPLE 2

Preparation of topical gel dosage form

Sl.No.	Component	Quantity
1.	Rofecoxib	2.00 g
2.	Dimethylacetamide	22.0 g
3.	Ethyl Alcohol	40.0 g
4.	Acetone	10.0 g
5.	Cremophor RH 40	4.0 g
6.	Propylene glycol	38.0 g
7.	Polyethylene glycol 400	48.8 g
8.	Carbopol 934	4.0 g
9.	Water	30.0 g
10.	Diethylamine	1.2 g
	Total	200.0 g

Step (a) Dimethylacetamide is mixed with ethyl alcohol and acetone at 30°C. in a container with stirring. To the mixture obtained Rofecoxib is added and stirred till completely dissolved.

Step (b) Propylene glycol, polyethylene glycol 400 and water are mixed in homogenizer. To the homogenised mixture obtained, 1.5% w/w of carbopol 934 is added in small amounts at a time at room temperature and the speed of the homogenizer is kept at approximately 1500 – 2000 rpm.

Step © The mixture obtained in step (a) is added to the mixture obtained in step (b) under stirring without vortex formation to avoid aeration preferably under vacuum (25 mm of Hg). The mixture obtained is neutralised by slow addition of diethylamine with slow stirring at a temperature of 25° - 30°C and under vacuum (25 mm of Hg) to affect gel formation.

EXAMPLE 3

Preparation of emulsion type topical dosage form

Sl.No.	Component	Quantity
1.	Rofecoxib	1.0 g
2.	Transcutol	35.0 g
3.	Water	10.0 g
4.	Disodium Hydrogen Phosphate	0.1 g
5.	Cremophor RH 40	5.0 g
6.	Labrafil M 1944 CS	10.0 g
7.	Glyceryl monostearate	8.0 g
8.	Stearic acid	13.0 g
9.	Ethyl oleate	2.9 g
10.	Diethyl Sulphoxide	15.0 g
	Total	100.0 g

Dissolve Rofecoxib in a mixture of (6), (7), (8), (9) and (10) with warming. Separately mix (2), (3), (4) and 5 and slowly add the Rofecoxib mixture to it with stirring.

EXAMPLE 4

Preparation of emulsion type topical dosage form

Sl.No.	Component	Quantity
1.	Celecoxib	1.0 g
2.	Transcutol	35.0 g
3.	Water	10.0 g
4.	Disodium Hydrogen Phosphate	0.1 g
5.	Cremophor RH 40	5.0 g
6.	Labrafil M 1944 CS	10.0 g
7.	Glyceryl monostearate	8.0 g
8.	Stearic acid	13.0 g
9.	Ethyl oleate	2.9 g
10.	Diethyl Sulphoxide	15.0 g
	Total	100.0 g

Dissolve Celecoxib in a mixture of (6), (7), (8), (9) and (10) with warming. Separately mix (2), (3), (4) and 5 and slowly add the Celecoxib mixture to it with stirring.

EXAMPLE 5

Preparation of solution type dosage form for topical application

Sl.No.	Component	Quantity
1.	Celecoxib	1.0 g
2.	Dimethyl formamide	10.0 g
3.	Poloxamer 188	2.0 g
4.	Ethyl alcohol	20.0 g
5.	Propylene glycol	25.0 g
6.	Polyethylene glycol 400	42.0 g
7.	Hydroxypropylmethyl cellulose	1.0 g
8.	Triethanolamine	0.2 g
9.	Water	1.0 g
	Total	100.0 g

Celecoxib is dissolved in (2) with stirring and (3), (4), (5), (6), (7) and (8) are added to obtain a clear solution with stirring.

EXAMPLE 6

Preparation of solution type dosage form for topical application

Sl.No.	Component	Quantity
1.	Rofecoxib	1.0 g
2.	Dimethyl formamide	10.0 g
3.	Poloxamer 188	2.0 g
4.	Ethyl alcohol	20.0 g
5.	Propylene glycol	25.0 g
6.	Polyethylene glycol 400	42.0 g
7.	Hydroxypropylmethyl cellulose	1.0 g
8.	Triethanolamine	0.2 g
9.	Water	1.0 g
	Total	100.0 g

Rofecoxib is dissolved in (2) with stirring and (3), (4), (5), (6), (7) and (8) are added to obtain a clear solution with stirring.

EXAMPLE 7

Preparation of ointment type dosage form topical application

Sl.No.	Component	Quantity
1.	Rofecoxib	2.0 g
2	Dimethylsulphoxide	21.0 g
3.	Glycerylmonostearate	16.0 g
4.	Mineral oil	62.0 g
5.	White Petrolatum	97.0 g
6.	Water	2.0 g
	Total	200.0 g

Warm (3), (4) and (5) and add with stirring a solution of Rofecoxib in dimethyl sulphoxide.

EXAMPLE 8

Preparation of ointment type dosage form topical application

Sl.No.	Component	Quantity
1.	Celecoxib	2.0 g
2	Dimethylsulphoxide	21.0 g
3.	Glycerylmonostearate	16.0 g
4.	Mineral oil	62.0 g
5.	White Petrolatum	97.0 g
6.	Water	2.0 g
	Total	200.0 g

Warm (3), (4) and (5) and add with stirring a solution of Celecoxib in dimethyl sulphoxide.

EXAMPLE 9

Preparation of an aerosol dosage form for topical use.

Sl.No.	Component	Quantity
1.	Celecoxib	1.0 g
2.	Dimethylacetamide	10.0 g
3.	Ethyl alcohol	10.0 g
4.	Cremophor RH 40	10.0 g
5.	Propellant 114	29.0 g
6.	Propellant 12	39.0 g
7.	Water	1.0 g
	Total	100.0 g

EXAMPLE 10

Preparation of an aerosol dosage form for topical use.

Sl.No.	Component	Quantity
1.	Rofecoxib	1.0 g
2.	Dimethylacetamide	10.0 g
3.	Ethyl alcohol	10.0 g
4.	Cremophor RH 40	10.0 g
5.	Propellant 114	29.0 g
6.	Propellant 12	39.0 g
7.	Water	1.0 g
	Total	100.0 g

EXAMPLE 11

Preparation of an aerosol dosage form .

Sl.No.	Component	Quantity
1.	Celecoxib	1%
2.	Methyl Salicylate	20%
3.	Eucalyptus	6%
4.	Clove oil	1%
5.	Menthol	4%
6.	Camphor	10%
7.	Cinnamon oil	0.5%
8.	Terpentine oil	10%
9.	Solvent	q.s to 100%

EXAMPLE 12

Preparation of an aerosol dosage form.

Sl.No.	Component	Quantity
1.	Rofecoxib	1%
2.	Methyl Salicylate	20%
3.	Eucalyptus	6%
4.	Clove oil	1%
5.	Menthol	4%
6.	Camphor	10%
7.	Cinnamon oil	0.5%
8.	Terpentine oil	10%
9.	Solvent	q.s to 100%

EXAMPLE 13

Topical Preparation

1.	Purified Water	q.s. 100 g
2.	Glycerin	3.00 g
3.	Cetostearyl alcohol	5.00 g
4.	Cetyl alcohol	2.00 g
5.	Oil of wintergreen	2.00 g
6.	Caprylic and capric triglyceride	1.80 g
7.	Rofecoxib	0.5 g
8.	Citrata oil	3.0 g
9.	Parabens	1.0 g
10.	Tocopherol-Ascorbyl palmitate soy lecithin	0.01 g
11.	Citric acid	0.02 g

Process:

Step 1. Mix 1 and 2 is a jacketted vessel.
Step 2. Mix ingredients 3 to 11 separately at 40 – 60°C
Step 3. Mix phases of step 1 and 2 using a homegenizer

EXAMPLE 14

	Topical Preparation	
1.	Purified Water	q.s. 100 g
2.	Glycerin	3.00 g
3.	Cetostearyl alcohol	5.00 g
4.	Cetyl alcohol	2.00 g
5.	Oil of wintergreen	2.00 g
6.	Caprylic and capric triglyceride	1.80 g
7.	Celecoxib	0.5 g
8.	Citrata oil	3.0 g
9.	Parabens	1.0 g
10.	Tocopherol-Ascorbyl palmitate soy lecithin	0.01 g
11.	Citric acid	0.02 g

Process:

Step 1. Mix 1 and 2 is a jacketted vessel.
Step 2. Mix ingredients 3 to 11 separately at 40 – 60°C
Step 3. Mix phases of step 1 and 2 using a homegenizer

Since many apparently different embodiments of the present invention could be made without departing from the spirit and scope thereof, it is intended that the description of the invention herein be interpreted as being illustrative only and not limiting in any manner whatsoever.

We Claim :

1. A therapeutic anti- inflammatory and analgesic pharmaceutical composition for topical /transdermal use which comprises :
Selective COX-2 inhibitor drugs from 0.1% to 40% w/w and
Percutaneous absorption enhancing vehicle/base from 60% to 99.9% w/w

2. A composition as claimed in claim 1 wherein said percutaneous absorption enhancing vehicle/base comprises:-

Percutaneous enhancer from 0.5% to 60% w/w and
Vehicle/base from 2.0% to 98%

3. A composition as claimed in claim 1 or 2 further comprising 0% to 60% w/w of the gelling agent/ thickening agent.

4. A composition as claimed in claim 1 or 2 further comprising 0% to 20% w/w of a surfactant.

5. A composition as claimed in claim 1 or 2 further comprising a neutralizing agent/pH adjusting agent in an amount 0 to 5% w/w.

6. A composition as claimed in claim 1 or 2 wherein the percutaneous enhancer is selected from the group which interacts with stratum comeum layer of the mammalian skin causing reversible change in its barrier properties.

7. A composition as claimed in claim 1 or 2 wherein the percutaneous enhancer is selected from sulphoxides, amides or pyrrolidones, laurocapram essential oils, or C_{12-24} mono or poly-unsaturated fatty acids or any of their corresponding alcohols.

8. A composition as claimed in claim 7 wherein the percutaneous enhancer is dimethylacetamide.

9. A composition as claimed in claim 4 wherein the surfactant is a pharmaceutically acceptable hydrophilic or lipophilic surfactant or mixture thereof.

10. A composition as claimed in claim 9 wherein the surfactant is selected from polyoxyethylene glycolated natural or hydrogenated castor oil, polyoxyethylene-sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block compolymers, polyoxyethylene fatty acids esters, propylene glycol mono-and di-fatty acid esters; lipophilic surfactants like sorbitan fatty acid esters, monoglycerides, sugar esters, transesterification products of natural vegetable oil triglycerides and alkylene polyols.

11. A composition as claimed in claim 3 wherein said gelling/thickening agent is selected from natural, synthetic or semi-synthetic polymeric materials, like polyacrylate and polyacrylate co-polymeric resins, cellulose and cellulose derivatives or polyvinyl resins.

12. A composition as claimed in claim 5 wherein the neutralizing/pH adjusting agent is selected from the group comprising sodium bicarbonate, sodium hydroxide, potassium hydroxide, borax, disodium hydrogen phosphate, sodium dihydrogen phosphate, hydrochloric acid, Lactic acid, phosphoric acid and malic acid.

13. A composition as claimed in claim 5 wherein neutralizing/pH adjusting agent is a polar organic amine.

14. A composition as claimed in claim 2 wherein the vehicle/base is selected from pharmaceutically acceptably lower (C_{1-5}) alkanols; water soluble macrogols; 1,2-propylene carbonate, Butylene glycol, polypropylene glycol, 1-2-propylene glycol, glycerol triacetate, glycerol, lower ketones, chlorofluorocarbons, hydrofluorocarbons, and water.

15. A therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical/ transdermal use which comprises :

Selective COX-2 inhibitor drugs: 0.1% to 40% w/w
Percutaneous enhancer : 0.5% to 60% w/w,
Gelling agent/thickening agent : 0% to 60% w/w,
Vehicle/base : 2% to 98% w/w
and 0 to 20% w/w of surfactant.

16. A therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical/ transdermal use which comprises :

Selective COX-2 inhibitor drugs : 0.1% to 40% w/w.

Percutaneous enhancer : 0.5% to 60% w/w.

Gelling agent/thickening agent : 0% to 60% w/w.

Vehicle/base : 2% to 98% w/w

and 0 to 20% w/w of surfactant, and 0 to 5% w/w of neutralizing/pH adjusting agent.

17. A composition as claimed in claim 1 wherein the Selective COX-2 inhibitor drugs are selective from the group comprising Celecoxib and Rofecoxib.

18. A process for the manufacture of a therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical/transdermal use which comprises mixing together in any convention manor 0.1% to 40% w/w of Selective COX-2 inhibitor drugs with 60% to 99.9% W/W of percutaneous absorbiton enhancing vehicle/base under ambient conditions.

19. A process for the manufacture of a therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical/transdermal use as claimed in claim 18 wherein the said percutaneous absorbiton enhancing vehicle/base comprises percutaneous enhancer from 0.5% to 60% w/w and

vehicle/base from 2.0% to 98%

20. A process for the manufacture of a therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical/transdermal use as claimed in claim 18 or 19 further comprising 0% to 60% w/w of the gelling agent/thickening agent.

21. A process for the manufacture of a therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical/transdermal use as claimed in claim 18 or 19 further comprising 0% to 20% w/w of a surfactant.

22. A process for the production of a therapeutic and analgesic pharmaceutical composition for topical/transdermal use as claimed in any of the preceding claims 18 or 19 which comprises :

(a) mixing 0.5% w/w to 60% w/w of a percutaneous enhancer with 2% to 98% w/w of one or more vehicles or bases ;

(b) adding to the mixture of step (a) 0.1% w/w to 40% w/w of Selective COX-2 inhibitor followed by stirring the mixture until completely dissolved :

(c) mixing separately 0% w/w to 20% w/w of a surfactant, 0% w/w to 60% of a gelling agent/ thickening agent and 2.0% w/w to 98% w/w of one or more vehicles or bases and mixing the entire mixture; and

(d) adding the mixture obtained in step (b) to the mixture obtained in step (c) under stirring to obtain the composition.

23. A process as claimed in claim 22 wherein a neutralizing agent or a pH adjusting agent is added to the composition in step (d) to neutralize or adjust the pH of the mixture.

24. A process as claimed in claim 23 wherein the said neutralizing agent/pH adjusting agent is added in an amount of up to 5.0% w/w.

25. A therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical/transdermal use substantially as herein described with reference to the foregoing description and the accompanying examples.

26. A process for the production of therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical/transdermal use substantially as herein described with reference to the foregoing description and the accompanying examples.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 July 2001 (26.07.2001)

PCT

(10) International Publication Number
WO 01/52897 A3

(51) International Patent Classification[7]: A61K 47/12, 47/10, 47/22, 47/18, 31/415

(21) International Application Number: PCT/IN01/00007

(22) International Filing Date: 19 January 2001 (19.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
46/DEL/2000 21 January 2000 (21.01.2000) IN

(71) Applicant *(for all designated States except US)*: **PANACEA BIOTEC LIMITED** [IN/IN]; B-1 Extn./A-27, Mohan Co-operative, Industrial Estate, Mathura Road, New Delhi 110 044 (IN).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SINGH, Amarjit** [IN/IN]; Panacea Biotec Limited, B-1 Extn./A-27, Mohan Co-operative, Industrial Estate, Mathura Road, New Delhi 110 044 (IN). **JAIN, Rajesh** [IN/IN]; Panacea Biotec Limited, B-1 Extn./A-27, Mohan Co-operative, Industrial Estate, Mathura Road, New Delhi 110 044 (IN).

(74) Common Representative: **JAIN, Rajesh**; Panacea Biotec Limited, B-1 Extn./A-27, Mohan Co-operative, Industrial Estate, Mathura Road, New Delhi 110 044 (IN).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
14 March 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/52897 A3

(54) Title: THERAPEUTIC ANTI-INFLAMMATORY AND ANALGESIC COMPOSITION CONTAINING SELECTIVE COX-2 INHIBITORS

(57) Abstract: A therapeutic anti-inflammatory and analgesic composition for topical/transdermal use which comprises: Selective Cox-2 inhibitor drugs from 0.1% to 40% w/w and percutaneous absorption enhancing vehicle/base from 60% to 99.9% w/w. Optionally Gelling agent/thickening agent (0% to 60% w/w) surfactant (0% to 20% w/w). Neutralizing agent/pH adjusting agent (0% to 5% w/w) may be added to the said composition.

INTERNATIONAL SEARCH REPORT

Inte .onal Application No
PCT/IN 01/00007

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/12 A61K47/10 A61K47/22 A61K47/18 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 812 587 A (PANACEA BIOTEC LTD) 17 December 1997 (1997-12-17) the whole document ---	1-16, 18-26
X	EP 0 782 855 A (HELSINN HEALTHCARE SA) 9 July 1997 (1997-07-09) the whole document --- -/--	1-7,9, 11, 13-16, 18,25,26

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

°A° document defining the general state of the art which is not considered to be of particular relevance

°E° earlier document but published on or after the international filing date

°L° document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

°O° document referring to an oral disclosure, use, exhibition or other means

°P° document published prior to the international filing date but later than the priority date claimed

°T° later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

°X° document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

°Y° document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

°&° document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 September 2001	18/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marttin, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/IN 01/00007

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 04019 A (BEECHAM GROUP PLC) 19 March 1992 (1992-03-19) page 1, line 1 - line 17 page 2, line 7 - line 34 page 4, line 6 -page 8, line 10 page 12, line 26 - last line; claims; examples 1-3	1-4,6,7, 9-11,14, 15, 18-21, 25,26
X	WO 00 00120 A (PRAECIS PHARM INC ;WILLIAMS C DONALD (US); MURDOCK ROBERT W (US)) 6 January 2000 (2000-01-06) claims 1,2,9,16-18,28-30,34,48-50; example 73 page 4, line 14 - line 18 page 5, line 12 - last line page 10, line 12 - line 31 page 11, line 27 -page 12, line 23 page 13, line 35 -page 14, line 10	1-4,6, 10,11, 15, 17-21, 25,26
X	EP 0 147 146 A (AMERICAN HOME PROD) 3 July 1985 (1985-07-03) page 3, line 7 - last line page 4, line 33 -page 5, last line; claims 1-4,7,8; example 3	1,2,6, 18,19, 25,26
X	WO 96 41626 A (SEARLE & CO) 27 December 1996 (1996-12-27) page 5, line 7 - line 16 page 7, line 30 -page 8, line 4 page 47, line 30 -page 49, line 29; claims 1,2	1,6,17, 25,26
X	WO 99 44640 A (MERCK SHARP & DOHME ;BOYCE SUSAN (GB)) 10 September 1999 (1999-09-10) claims 1,3,4; example 3 page 1, line 4 - line 6 page 3, line 13 -page 4, line 6 page 4, line 15 - line 28 page 7, line 6 - line 20 -/--	1,6,17

2

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/IN 01/00007

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	CRYER B ET AL: "The advent of highly selective inhibitors of cyclooxygenase-a review - Implications for gastrointestinal toxicity" PROSTAGLANDINS AND OTHER LIPID MEDIATORS, BUTTERWORTH, STONEHAM, MA, US, vol. 56, no. 5-6, August 1998 (1998-08), pages 341-361, XP004156755 ISSN: 0090-6980 page 342, line 14 - line 34; table 1 page 351, line 21 -page 353, last line; table 3 ---	1-26
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1995 SPANGLER R S: "New insight into NSAID-induced gastropathy." Database accession no. PREV199698736774 XP002176551 abstract & INFLAMMOPHARMACOLOGY, vol. 3, no. 4, 1995, pages 347-350, ISSN: 0925-4692 -----	1-26

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-24 relate to a product or method defined by reference to a desirable characteristic or property, namely selective COX-2 inhibitor drugs. The term "selective COX-2 inhibitor drugs" defines the active agent by the selectivity of its enzyme inhibition. However, a compound canot be sufficiently characterised by the selectivity of its enzyme inhibition as it is done by an expression like "selective COX-2 inhibitor drugs", because it is impossible to know which substances are encompassed in this expression.

The claims cover all products or methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/compounds/methods/apparatus. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the products or methods by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products or methods mentioned in claim 17, examples 1-14, and the concept of selective COX-2 inhibitor drugs.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inte onal Application No
PCT/IN 01/00007

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0812587 A	17-12-1997	AU 696767 B	17-09-1998
		CA 2186919 A	01-04-1998
		CZ 9603165 A	13-05-1998
		HU 9601443 A	28-04-1998
		JP 3056694 B	26-06-2000
		JP 10139661 A	26-05-1998
		NO 302334 B	23-02-1998
		NZ 299500 A	24-02-1997
		AU 6796096 A	09-04-1998
EP 0782855 A	09-07-1997	AU 701740 B	04-02-1999
		AU 3619295 A	02-05-1996
		BG 101526 A	30-01-1998
		BR 9509183 A	30-12-1997
		CZ 9701703 A	14-01-1998
		DE 782855 T	28-05-1998
		EE 9700123 A	15-12-1997
		FI 972362 A	25-07-1997
		WO 9712608 A	10-04-1997
		JP 2894843 B	24-05-1999
		LT 97100 A,B	29-12-1997
		LV 11966 A	20-02-1998
		LV 11966 B	20-04-1998
		NO 972537 A	04-06-1997
		NZ 327092 A	29-09-1999
		PL 320534 A	13-10-1997
		RO 116040 B	30-10-2000
		SI 9620016 A,B	31-12-1997
		SK 70497 A	08-10-1997
		TR 9700409 T	23-08-1999
		US 5837735 A	17-11-1998
		CA 2201722 A	18-04-1996
		ES 2110375 T	16-02-1998
		WO 9611002 A	18-04-1996
WO 9204019 A	19-03-1992	AU 651619 B	28-07-1994
		AU 8494591 A	30-03-1992
		CA 2090974 A	06-03-1992
		EP 0548145 A	30-06-1993
		IE 913096 A	11-03-1992
		JP 6500778 T	27-01-1994
		ZA 9106967 A	26-08-1992
WO 0000120 A	06-01-2000	AU 4841599 A	17-01-2000
		BR 9912508 A	02-05-2001
		EP 1093348 A	25-04-2001
		NO 20006604 A	28-02-2001
EP 0147146 A	03-07-1985	AU 3683484 A	27-06-1985
		CA 1238275 A	21-06-1988
		DK 626384 A	23-06-1985
		GR 81250 A	19-11-1985
		HU 37040 A	28-11-1985
		JP 60152413 A	10-08-1985
		KR 8900183 B	09-03-1989
		US 4931283 A	05-06-1990
		US 4933184 A	12-06-1990
		ZA 8409780 A	27-08-1986

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/IN 01/00007

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9641626 A	27-12-1996	AU 6111796 A	09-01-1997
		CA 2224517 A	27-12-1996
		EP 0833622 A	08-04-1998
		JP 11507670 T	06-07-1999
		US 6136839 A	24-10-2000
WO 9944640 A	10-09-1999	AU 2632999 A	20-09-1999
		EP 1058559 A	13-12-2000